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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/700,806	03/12/2002	Ben-Quan Shen	P1735R1	4225

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EXAMINER	
HUNNICUTT, RACHEL KAPUST	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 02/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/700,806	SHEN ET AL.	
	Examiner	Art Unit	
	Rachel K. Hunnicutt	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,8,10,14-17,19 and 21-31* is/are pending in the application.

4a) Of the above claim(s) *16,17 and 31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,8,10,14,15,21-24 and 26-30* is/are rejected.

7)☒ Claim(s) *19 and 25* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 November 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1104*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. This application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid. The Information Disclosure Statement, mailed November 22, 2004, has been entered into the record.

Claims 16, 17, and 31 are withdrawn as being drawn to a non-elected species. Claims 1, 8, 10, 14-15, 19, and 21-30 are under consideration.

Claim Rejections - 35 USC § 112

Claims 1, 8, 10, 22-24, and 26-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating hypertension, thrombosis, angina, atherosclerosis, or heart failure, does not reasonably provide enablement for a method of treating diabetes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention; 2) state of the prior art; 3) relative skill of those in the art; 4) level of predictability in the art; 5) existence of working examples; 6) breadth of claims; 7) amount of direction or guidance by the inventor; and 8) quantity of experimentation needed to make and/or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims are drawn to methods of treating diabetes, a nitric oxide associated disorder, by administering an effective amount of a VEGF receptor agonist that is selective for a KDR receptor. The goal of the treatment is to stimulate sustained production of endogenous nitric oxide. Nitric oxide is involved in the destruction of β-cells during the development of type I diabetes mellitus (see El-Mahmoudy *et al.* (2005), *Int. Immunopharm.* 5: 195-207). El-Mahmoudy *et al.* teach that nitric oxide is a toxic agent that is a primary toxic effector molecule in the lysis of islet cells (p. 196). El-Mahmoudy *et al.* further teach that by inhibiting nitric oxide

synthase, one could partially suppress the development of diabetes mellitus (p. 196). Thus, increasing the production of nitric oxide would actually be detrimental and not helpful in the treatment of diabetes. One skilled in the art would not know how to increase the production of nitric oxide and treat diabetes.

Claims 1, 8, 10, 14, 15, 21, 22, and 26-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for VEGF variants having one or more amino acid substitutions at residues 63, 64, 65, 66 or 67, does not reasonably provide enablement for VEGF variants having one or more amino acid substitutions in a loop containing FLT-1 contact residues. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicants argue that the claims are fully enabled because their scope reasonably correlates with the enablement provided by the disclosure (p. 8 of response filed November 22, 2004). Applicants argue that they have provided extensive guidance as to the nature of mutations that can be made, they have disclosed the regions of VEGF which are important for binding to a KDR receptor and a FLT-1 receptor, and even an extended period of experimentation would not be undue because the skilled artisan is given sufficient direction and guidance.

Applicants' arguments have been fully considered but have not been found to be persuasive. In order for the VEGF variant to be effective, either residue 63, 64, 65, 66 or 67 must have a mutation, yet the claims do not have this requirement. One of skill in the art would not expect a VEGF variant not having a mutation at residue 63, 64, 65, 66 or 67 to be selective for a KDR receptor. In order for one skilled in the art to use the claimed invention, the VEGF variant must be mutated at residue 63, 64, 65, 66 or 67. One skilled in the art would not know how to use such VEGF variants which are encompassed by the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 8, 10, 14, 15, 21, and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Keyt *et al.* (1996, *J. Biol. Chem.* 271(10): 5638-5646, cited in September 2002 IDS) and further in view of Meyer *et al.* (1999, *The EMBO Journal* 18(2): 363-374, cited in September 2002 IDS). Claims 1, 8, 10, 21, and 22 are drawn to methods of treating hypertension, angina, thrombosis, heart failure or atherosclerosis by administering a VEGF receptor agonist that exhibits selective binding affinity for a KDR receptor. Claims 14 and 15 are drawn to methods of stimulating the sustained production of NO in an endothelial cell by administering a VEGF receptor agonist that exhibits selective binding affinity for a KDR receptor.

Keyt *et al.* teach VEGF receptor agonists that exhibit selective binding affinity for KDR receptors. Keyt *et al.* teach that mutating residues 63, 64, or 67 of VEGF to alanine results in a 30-fold decrease in affinity to the FLT-1 receptor (p. 5645, column 1). However, Keyt *et al.* do not teach administering the variants for the treatment of hypertension, angina, thrombosis, heart failure or atherosclerosis.

Meyer *et al.* teach that VEGF-E is selective for the KDR receptor, that it possesses an angiogenic activity as potent as VEGF, and because it does not bind Flt-1, VEGF-E's effective local concentration available for binding to the KDR receptor may increase (p. 370, column 2). Meyer *et al.* also teach that VEGF-E, a KDR receptor-selective VEGF agonist, is a novel candidate for the treatment of coronary heart disease or critical limb ischemia (p. 371, column 1). It would have been obvious to one of skill in the art to substitute the VEGF receptor agonists that are selective for the KDR receptor of Keyt *et al.* for VEGF-E as a potent angiogenic factor in the treatment of coronary heart disease or atherosclerosis associated with critical limb ischemia. One of skill in the art would have been motivated to do so because both proteins are selective for the KDR receptor, and the skilled artisan would expect the VEGF variants to be as effective in promoting angiogenesis as VEGF-E. At the time of the invention, it was commonly known in the art that the angiogenic properties of VEGF were useful in the treatment of hypertension, thrombosis, angina, and heart failure as well (see, for example, Van Belle *et al.* (1997), *Biochem. Biophys. Res. Comm.* 235: 311-316, Losordo *et al.* (1998), *Circulation*, 98: 2800-2804, Rosengart *et al.* (1999), *Circulation* 100: 468-474, and Isner *et al.* (1999), *Nat. Med.* 5(5): 491-492).

Meyer *et al.* and Keyt *et al.* are both silent as to the effect of VEGF on the production of NO. However, such a property is an inherent feature of VEGF and the KDR receptor. Kroll *et al.* (1998, *Biochem. Biophys. Res. Comm.* 252: 743-746) teach that VEGF induces expression of eNOS and iNOS via the KDR receptor. Thus, during the process of treating an individual for hypertension, angina, thrombosis, heart failure or atherosclerosis, the VEGF receptor agonists selective for the KDR receptor would induce expression of eNOS and iNOS.

Conclusion

Claims 19 and 25 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claims 1, 8, 10, 14, 15, 21-24, and 26-30 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rachel K. Hunnicutt whose telephone number is (571) 272-0886. The examiner can normally be reached on Mon-Fri 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

RKH
2/18/05

JANET ANDRES
PRIMARY EXAMINER